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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/687,402 | 10/16/2003 | Jaya Sivaswami Tyagi | AP35478 066123.0125 | 8618 |

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| EXAMINER | |
|---|---|
| FERNANDEZ, SUSAN EMILY | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1651 | |

DATE MAILED: 08/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/687,402 | TYAGI ET AL. | |
| | Examiner | Art Unit | |
| | Susan E. Fernandez | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The amendment filed May 31, 2005, has been received and entered. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claims 1-6 are pending and are presented for examination.

### *Claim Objections*

Claim 6 is objected to because of the following informalities: At line 2, claim 6 recites "an-activity" though claim 6 filed on October 16, 2003, recited "an activity". Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the recitation "SDS-PAGE based high throughput assay" in claim 1 lacks support in the disclosure as filed. Assays discussed in the disclosure were SDS-PAGE **or** high throughput assays, and no instances were disclosed of SDS-PAGE based high throughput assays.

The DevB protein recited in claim 1, section c, part i, also lacks support in the disclosure. It appears that the recitation "DevB" should be substituted with "DevS".

Additionally, the specification as filed contains no limitations of the determination of the drug potential of the test compound wherein the potency of the drug is inversely proportional to "the degree of phosphotransfer from phosphorylated DevS, and Rv2027 proteins to DevR". Instead of the limitation recited in part ii of section c in claim 1, the disclosure indicates that the potency of the drug is inversely proportional to "the degree of phosphotransfer-based dephosphorylation of DevR and its single domain derivative" (page 25, paragraph [0059]), thus implying phosphotransfer from phosphorylated DevR, where the recipient(s) is not disclosed. Furthermore, the specification does not disclose the determination of the drug potential of the test compound wherein the potency of the drug is inversely proportional to "the degree of loss of phosphate-associated radioactivity from DevS/Rv2027c and DevR in a reaction containing DevS, DevR/Rv2027 and DevR," recited in claim 1, section c, part iii. In sum, because the specification as field fails to provide clear support for the new claim language, a new matter rejection is clearly proper.

***Claim Rejections - 35 USC § 103***

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoch et al. (US Patent 6,043,045) in view of Dasgupta et al. (2000, Tubercle and Lung Disease, 80(3): 141-159).

Hoch et al. discloses a method for identifying new antibiotic, antibacterial, or antimicrobial agents by inhibition of bacterial two-component systems. Specifically, agents are

sought that cause the "inhibition of either the autophosphorylation or the subsequent phosphor-transfer" (column 2, lines 16-23). Furthermore, the conventional use of SDS-PAGE to assay two-component systems is described (column 2, lines 24-35), where autoradiographic analysis is used. The use of SDS-PAGE with multiple samples can be interpreted as "SDS-PAGE based high throughput assaying". Hoch et al. provides a high-throughput screening assay for histidine protein kinase for agent identification (column 22, lines 16-24), as described in Example 1 starting at lines 30 of column 15. In this high-throughput screening assay, the histidine protein kinase (KinA) and its substrate (SpoOF) are expressed in *E.coli* and purified (column 15, lines 45-47). This can be considered the overexpression of the histidine protein kinase. This high-throughput screening assay measures the extent of phosphorylation of the substrate and the radioactivity remaining on a resin (column 2, lines 50-53 and column 17, lines 43-45) following SDS-PAGE analysis.

Hoch et al. does not expressly disclose the use of their methods for inhibition of DevR-DevS or DevR-Rv2027c and its homologues nor does it disclose the identification of anti-tuberculosis and anti-mycobacterial compounds. Additionally, Hoch et al. does not disclose the relation between the potency of a drug and the degree of phosphotransfer and loss of phosphate-associated radioactivity as recited in claim 1, section c, parts ii and iii.

Dasgupta et al. discloses the DevR-DevS two-component system in mycobacteria, specifically *M. tuberculosis*, as well as the homology of Rv2027c with DevS. It is obvious that $DevS_{578}$, $Rv2027_{194}$, and $DevRN_{145}$ would share common characteristics with DevS, Rv2027 and DevR respectively because, as evidenced by Dasgupta (Figure 3, page 148 and Figure 5, page

150), the claimed portions each contain the catalytic site of the molecules, based on the size of the transcripts disclosed in the reference.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to apply the methods of Hoch et al. to the DevR-DevS and the known homolog of DevR-Rv2027c as described in Dasgupta et al. The DevR-DevS and DevR-Rv2027c systems both comprise a histidine protein kinase (DevS or Rv2027c), thus being appropriate as a target of the Hoch invention. By applying the Hoch invention to the DevR-DevS system, it would be obvious that an agent positively identified could be used for tuberculosis or other diseases caused by mycobacteria.

One of ordinary skill in the art would have been motivated to do this because Dasgupta et al. concludes that "the devR-devS two-component system may thus serve as a novel target for anti-tubercular therapy" (page 158, second paragraph). Tuberculosis is a critical issue, so there is a high incentive to develop or determine compounds for its treatment. There would have been a reasonable expectation of success that the Hoch invention could be used for bacteria such as *M. tuberculosis* that have DevR-DevS and/or DevR-Rv2027c and its homologues based on the fact that Hoch's assay techniques are disclosed as measuring the same reactions catalyzed by Dasgupta's tuberculosis phosphorylases. Finally, it would have been obvious to have expected the same correlation between drug potency and phosphotransfer and radioactivity as recited in claim 1, section c. The degree of phosphotransfer and loss of phosphate-associated radioactivity would have inherently occurred when using the histidine protein kinase system of the claims, as the Hoch reference and the claims under examination use the same processes. A holding of obviousness is therefore proper.

Applicant's arguments filed May 31, 2005, have been fully considered but they are not persuasive. Applicant indicates that in Hoch et al. is based on distinct principles and compositions. However, it is respectfully pointed out that Hoch et al. is applied in combination with Dasgupta et al., which teaches the devR-devS two-component system composition recited in the claims. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that Hoch et al. is based on distinct principle from the claims under examination, it is not clear that the principles used in both inventions are different, as the DevR-DevS and DevR-Rv2027c systems would have substituted KinA in practicing the Hoch invention, thus serving as the "sensor" as described on page 8 of the Response. Even if DevS is the "sensor", applicant provides no evidence that the Hoch invention would not have yielded the same results as would have been obtained with the invention under examination. With respect to the applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., no separation of DevR from DevS) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Finally, applicant indicates that there are significant variations among individual two-component kinase systems in terms of the kinetics of phosphorylation, half-lives of the phosphorylated form of the proteins and the mechanism of dephosphorylation of the response regulator components. Furthermore, applicant indicates that "these factors are critical in

determining whether a particular system might be amenable to a specific utility..." (page 8, last paragraph) and that one of ordinary skill would not have been motivated to combine the assay of the Hoch patent to the DevR-DevS two component system due to shared phosphorylation reactions. The examiner respectfully disagrees as Hoch et al. specifies that "it should be appreciated...that the disclosed assay systems can also be applied to other protein kinases and their substrates" (column 2, lines 65-67). Additionally, as discussed above, one would have been motivated to apply the Hoch methods to the DevR-DevS system since it may serve as a novel target for anti-tubercular therapy. Therefore, the holding of obviousness is properly maintained.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan E. Fernandez whose telephone number is (571) 272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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sef

FRANCISCO PRATS
PRIMARY EXAMINER